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CASE REPORT

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A novel frameshift *GRN* mutation results in frontotemporal lobar degeneration with a distinct clinical phenotype in two siblings: case report and literature review

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Abstract

Background: Progranulin gene (*GRN*) mutations are major causes of frontotemporal lobar degeneration. To date, 68 pathogenic *GRN* mutations have been identified. However, very few of these mutations have been reported in Asians. Moreover, some *GRN* mutations manifest with familial phenotypic heterogeneity. Here, we present a novel *GRN* mutation resulting in frontotemporal lobar degeneration with a distinct clinical phenotype, and we review reports of *GRN* mutations associated with familial phenotypic heterogeneity.

Case presentation: We describe the case of a 74-year-old woman with left frontotemporal lobe atrophy who presented with progressive anarthria and non-fluent aphasia. Her brother had been diagnosed with corticobasal syndrome (CBS) with right-hand limb-kinetic apraxia, aphasia, and a similar pattern of brain atrophy. Laboratory blood examinations did not reveal abnormalities that could have caused cognitive dysfunction. In the cerebrospinal fluid, cell counts and protein concentrations were within normal ranges, and concentrations of tau protein and phosphorylated tau protein were also normal. Since similar familial cases due to mutation of *GRN* and microtubule-associated protein tau gene (*MAPT*) were reported, we performed genetic analysis. No pathological mutations of *MAPT* were identified, but we identified a novel *GRN* frameshift mutation (c.1118_1119delCCinsG: p.Pro373ArgX37) that resulted in progranulin haploinsufficiency.

Conclusion: This is the first report of a *GRN* mutation associated with familial phenotypic heterogeneity in Japan. Literature review of *GRN* mutations associated with familial phenotypic heterogeneity revealed no tendency of mutation sites. The role of progranulin has been reported in this and other neurodegenerative diseases, and the analysis of *GRN* mutations may lead to the discovery of a new therapeutic target.

Keywords: Progranulin, Primary progressive aphasia, Corticobasal syndrome, Frontotemporal lobar degeneration, Phenotypic heterogeneity, Case report

Background

Frontotemporal lobar degeneration (FTLD) is characterized by degeneration of the frontal and temporal lobes, and presents as a clinically heterogeneous disease. The pathological classification of FTLD is based on the molecular features of the disease-associated inclusion-

forming proteins: FTLT-tau, FTLT-TDP, FTLT-FUS, and FTLT-UPS. Clinically, FTLD is classified into two subsets: behavioral variant FTLD (bvFTLD) and primary progressive aphasia (PPA), the latter of which includes semantic dementia and progressive non-fluent aphasia. In addition, FTLD can be concomitant with corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and motor neuron disease (MND) [1].

Progranulin is widely expressed in the central nervous system and is involved in immunomodulation as well as cell growth and proliferation. Since the first demonstration of

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FTLD-associated progranulin gene (*GRN*) mutation in 2006 [2, 3], more than 150 *GRN* mutations have been identified, including 68 pathogenic mutations. FTLD due to a *GRN* mutation is histopathologically characterized by ubiquitin-positive and TDP-43-positive inclusion bodies. While the most frequent clinical phenotype is bvFTLD, PPA and corticobasal syndrome (CBS) have also been reported [4–6]. There are also reports of clinical heterogeneity within a family [7, 8]. In addition, FTLD due to a *GRN* mutation is rare in Asian individuals, with an incidence of <1% in Asians compared to an incidence of 5–10% in Europeans [9, 10].

In this report, we present the case of a 74-year-old Japanese woman with left-side atrophy in the frontal and temporal lobes and symptoms of progressive anarthria and non-fluent aphasia. We identified the cause to be a novel frameshift mutation in *GRN* that caused progranulin haploinsufficiency.

Case presentation

A 74-year-old woman was referred to our hospital and admitted for progressive speech and language difficulties. The patient was unable to recall the names of things or persons and was unable to communicate with others for about 1 year prior to admission, though she was able to shop and do housework without difficulty. She had no significant medical history; however, regarding her family history, her elder brother had developed word-finding difficulty with verbal paraphasia and right-hand limb-kinetic apraxia at the age of 62 years of age, and was

diagnosed with CBS at 69 years of age. He had frontal lobe signs such as forced grasping, total aphasia, and right-limb kinetic apraxia; moreover, brain magnetic resonance imaging (MRI) demonstrated frontal and temporal lobar atrophy dominantly affecting the left side (Fig. 1a). The patient's brother and parents had passed away; therefore, we could not obtain their detailed clinical information.

Neurological findings indicated that our patient was lucid, but showed thought laziness. The cranial nerves, including those related to eye movement, were normal. The patient had normal muscle tone and did not show muscle weakness or involuntary movement, but all extremity tendon reflexes were slightly increased. There was no evidence of sensory impairment or cerebellar ataxia. It was noted that speech required significant effort, was slow and non-fluent, and showed anarthria and aphasia. The patient's Mini-Mental Scale Examination score was 4/30.

Language function was assessed using the Western Aphasia Battery (WAB) Japanese edition once and SLTA (standard language test of aphasia) two times within 2 months. The scores of WAB subtests were as follows: spontaneous speech, 13 points; auditory verbal comprehension, 5.5 points; repetition, 0 points; naming, 0 points; reading, 4.3 points; writing, 2.2 points; praxis, 6.8 points; and construction, drawing, block design & calculation, 6.6 points. Raven's score was 25/37 (average \pm standard deviation: 26.9 \pm 5.4). Aphasia quotient was 36.8. The results of SLTA were similar to those of

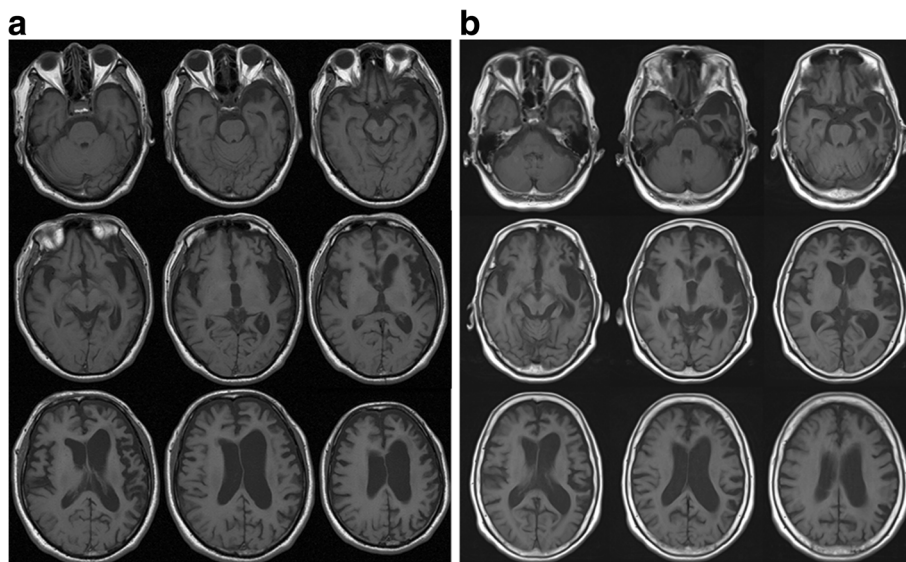


Fig. 1 Brain MRI (axial T1-weighted images) of the patient's brother (**a**) and the patient (**b**). **a** T1-weighted brain images of the patient's brother at 4 years after disease onset. Atrophy was predominantly observed in the left hemisphere affecting the frontotemporal lobes. **b** T1-weighted brain images of the patient at 1 year after disease onset. Similar to her brother, atrophy was predominantly observed in the left hemisphere affecting the frontal and temporal lobes

Table 1 Familial cases presenting with distinct clinical phenotypes

Case	Age onset; number of patients	First symptom	Phenotype	Brain atrophy	Ethnic origin	<i>GRN</i> mutation
Rovelet-Lecrux et al., 2008 [15]	67,77; 2 patients	Language dysfunction Resting tremor	PPA PD	left > right	French	g.95_4390del
Spina et al., 2007 [13]	45,73; 2 patients	Involuntary arm movement Cognitive decline	CBS AD	right > left	N/A	g.26C > A
Beck et al., 2008 [4]	54–67; 10 patients	Language dysfunction Limb apraxia	PPA CBS	left > right (n = 2) right > left (n = 1)	United Kingdom	g.90_91insCTGC
Skoglund et al., 2009 [12]	46–59; 10 patients	Language dysfunction Limb apraxia	PPA CBS	N/A	Swedish	g.102delC
Rademakers et al., 2007 [16]	62,66; 2 patients	N/A	FTLD, CBS	N/A	American	g.3240C > T
Masellis et al., 2006 [17]	57,62; 2 patients	Behavioral changes Axial and extremity rigidity	FTLD CBS	right > left	Canadian family of Chinese origin	g.1637G > A
Leverenz et al., 2007 [18]	35–69; 9 patients	Language dysfunction Anxiety, apathy Parkinsonism	FTLD PPA PD	left > right (n = 3) right > left (n = 1)	American	g.1871A > G
López de Munain et al., 2008 [19]	53,57; 2 patients	N/A	FTLD, CBS	N/A	Basque Country	g.1872G > A
	51,71; 2 patients	N/A	FTLD, CBS	N/A	Basque Country	g.1873G > A
	65; 2 patients	N/A	FTLD, CBS	N/A	Basque Country	g.1874G > A
	60; 2 patients	N/A	FTLD, CBS	N/A	Basque Country	g.1875G > A
	63–70; 4 patients	N/A	FTLD, CBS	N/A	Basque Country	g.1876G > A
Benussi et al., 2009 [5]	60–71; 5 patients	Language dysfunction	PPA	right > left	Italian	g.1977_1980delCACT
		Parkinsonism	CBS			
Kelley et al., 2009 [6]	N/A; 6 patients	N/A	FTLD, PD	symmetrical	American	g.2273_2274insTG
	N/A; 6 patients	N/A	FTLD, PD	right > left	American	g.2597delC
Pietroboni et al., 2011 [7]	47–79; 5 patients	Memory impairment, Acalculia	FTLD, AD	right > left (n = 1) symmetrical (n = 1) N/A (n = 3)	Italian	g.63_64insC
		Language impairment				
Rossi et al., 2011 [8]	47–80; 6 patients	Behavioural abnormality Language dysfunction Attention impairment	FTLD Dementia	Left > right	Italian	g.1761_1762delCA
The present case	75,62; 2 patients	Language dysfunction Limb apraxia	PPA CBS	left > right	Japanese	g.1118_1119delCCinsG

AD Alzheimer's disease, ALS amyotrophic lateral sclerosis, CBS corticobasal syndrome, FTLD frontotemporal lobar degeneration, *GRN* progranulin gene, N/A not available, PD Parkinson's disease, PPA primary progressive aphasia

analysis. Table 1 provides a summary of known cases of *GRN* mutations that have been associated with familial phenotypic heterogeneity. The presence of familial phenotypic heterogeneity with respect to symptoms such as cognitive dysfunction and motor impairment has been reported in 17 families with *GRN* mutations [4–10, 12–19].

These studies reported significant variations in age of onset and mutation site, and motor neuron diseases were relatively uncommon. Families have also been reported with differing symptom laterality and different regions of brain atrophy. In a genetic analysis of 48 Japanese families with FTLD, PSP, or CBS [10], only one FTLD case with a *GRN*

mutation was identified. Therefore, familial FTLN associated with *GRN* mutations is very rare. Furthermore, our report is the first to describe in detail distinct phenotypes within a family. Additional investigations of *GRN* mutations mediating different clinical phenotypes of neurodegeneration within a family are necessary.

As mentioned above, haploinsufficiency is thought to underlie the mechanism of *GRN* mutation-associated FTLN. Haploinsufficiency is a cause of autosomal genetic conditions when the protein expressed by a single allele is not sufficient to maintain its normal function (loss of function) [20]. On the other hand, in many autosomal dominant conditions, toxic gain of function or toxicity of excessive proteins are the cause of disease [21, 22]. In fact, an approximate 50% decrease in mRNA and 33% decrease in progranulin protein was reported in one *GRN* mutation carrier [1, 2]. It has thus been suggested that an effective therapeutic strategy would be to increase progranulin levels in patients [1]. The relationship between *GRN* genetic variability and the risk of developing a neurodegenerative disease such as AD or MND has been reported [1]. Yet, the exact functions of progranulin in the brain remain unclear, and its pathogenic involvement in neurodegenerative disorders is not known. Therefore, the accumulation of new cases of *GRN* mutations that display distinct clinical phenotypes within a family may be helpful not only for the elucidation of progranulin function, but also for the development of replacement therapies in FTLN and other neurodegenerative diseases due to *GRN* mutations.

Abbreviations

AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; bvFTLN: Behavioral variant frontotemporal lobar degeneration; CBD: Corticobasal degeneration; CBS: Corticobasal syndrome; CJD: Creutzfeldt–Jakob disease; DNA: Deoxyribonucleic acid; FTLN: Frontotemporal lobar degeneration; *GRN*: Progranulin gene; *MAPT*: Microtubule-associated protein tau gene; MND: Motor neuron disease; MRI: Magnetic resonance imaging; PCR: Polymerase chain reaction; PD: Parkinson's disease; PPA: Primary progressive aphasia; PSP: Progressive supranuclear palsy; RNA: Ribonucleic acid; RT-PCR: Reverse transcriptase–polymerase chain reaction

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

TH and KI collected the clinical data, interpreted the data, and wrote the manuscript. KI recruited the patients and designed the manuscript. AT and KI performed the clinical data analysis and evaluation. TM, NM, KK, and TI analyzed

genomic DNA and mRNA of the patient's blood sample. All authors read and approved the final version of manuscript.

Ethics approval and consent to participate

The authors declare that ethics approval was not required for this case report.

Consent for publication

Written informed consents for the patient and her brother were obtained from the patient's husband for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests

The authors declare that they have no competing interests.

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